COVID-19 in Italian patients with rheumatic autoimmune systemic diseases

We followed with great interest the numerous reports published by the *Annals*[1–9] as regards the impact of the COVID-19 pandemic on different rheumatic autoimmune systemic diseases (ASD), including the survey study by Costa *et al*[9] that underlined the usefulness of telerheumatology in the management of patients with psoriatic arthritis in COVID-19 era. On the same topic, the world literature encompasses a large number of anecdotal observations, cohort studies and telephone surveys.[1–15] Overall, the observed prevalence of symptomatic COVID-19, usually as mild-moderate disease, in patients with chronic arthritis was comparable to that found in the general population, while worse outcomes represented almost rare events.[1–15] Conversely, increased percentages of symptomatic COVID-19 were observed in patient cohorts with connective tissue diseases, especially systemic lupus or systemic vasculitis.[6 7] Of note, in ASD complicated by COVID-19, the baseline use of immune modifiers, namely, conventional synthetic (csDMARD), biological (bDMARD) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARD), was not associated with worse COVID-19 disease outcomes.[3–5 9 10] Almost invariably these monocentre studies focused on ASD patients' populations from limited geographical areas.[1–15] Given the heterogeneous distribution of pandemic infection within the same country, we investigated the impact of COVID-19 in ASD patients' populations from three distinct regions of Italy (northern, Emilia Romagna; central, Tuscany; and southern, Calabria), characterised by different spread of the COVID-19 pandemic, prevalent in northern Italy with a marked gradient north-south.[16] Our 6-week multicentre telephone survey of 1641 unselected patients with ASD confirmed the quite benign clinical course of COVID-19 in ASD, along with the safety of baseline use of either bDMARD or tsDMARD[1–15]; however, the survey revealed a significantly higher prevalence of (1) either *definite COVID-19* (always confirmed by positive oral/nasopharyngeal swabs at PCR testing) or *highly suspected COVID-19* (presence of fever and/or known contact with infected subject, and at least 4 out of 12 typical signs/symptoms of COVID-19) in patients with ASD compared with the Italian, or regional, general population; (2) *definite COVID-19* plus *highly suspected COVID-19* in connective tissue diseases (CTD)/vasculitis (703 patients) compared with the subgroup of chronic arthritis (938 patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis); and (3) *definite COVID-19* plus *highly suspected COVID-19 in* ASD patients without ongoing csDMARD.[16]

Although a number of issues still remain to be better investigated, we can draw some provisional considerations based on the whole of currently available data:

- The actual prevalence of COVID-19 in patients with ASD might be underestimated, possibly due to concurrent factors, mainly the high rate of mild COVID-19 variants, the frequent clinical overlapping between ASD and COVID-19, and the limited availability of virological test that may be critical for differential diagnosis in many individuals.
- Despite increased susceptibility to infections that characterise patients with ASD, the impact of the COVID-19 pandemic revealed less severe than initially feared, particularly in countries with well-organised healthcare systems. It is very likely that the patients' awareness of the risks inherent to their chronic illness along with the disease-related physical limitations have conditioned the patients' lifestyle and reduced the probability of contracting COVID-19.
- In this context, the telemedicine applications may play an important role in the care of 'frail patients' in general, and patients with ASD in particular, during the COVID-19 pandemic peak or its possible re-exacerbation.
- The treatment with immune modifiers, that is, csDMARD, bDMARD and/or tsDMARD, commonly used in patients with chronic arthritis, has proven to be quite safe, even if available data warrant closer surveillance of patients with ASD on chronic immune-modulating treatments. On the other hand, these drugs might play some protective role against the most harmful manifestations of COVID-19 such as pneumonia and acute respiratory distress syndrome secondary to the cytokine storm. The results of ongoing trials to assess the efficacy and the correct timing in the introduction of antirheumatic drugs in patients with COVID-19 could clarify these important issues. On the basis of indirect observations suggested by real-life experience, ongoing chronic treatments with one or more immune modifiers at the time of COVID-19 infection (hydroxychloroquine, methotrexate, tocilizumab or baricitinib) might damper or prevent the more severe COVID-19 manifestations. The observed therapeutic failure of these drugs, introduced after the clinical onset of COVID-19 manifestations, could be related to their prolonged latency of action, while the employed high dosages may be responsible of frequent serious side effects.
- Noteworthy, patients with CTD/vasculitis compared with different chronic arthritis (rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis) showed a higher prevalence of COVID-19, as possible consequence of deeper immune-system dysfunction present in these disorders. Therefore, the heterogeneous subgroup of CTD/vasculitis should deserve well-tailored management strategies in the COVID-19 era.
- The epidemiology of this novel coronavirus is little known as regards the course of the ongoing pandemic, possible re-exacerbations and/or new waves.[17] In addition, possible virus-driven immune-mediated organ damages as delayed COVID-19 manifestations cannot be ruled out at all, particularly in individuals with basically altered immune reactivity. Although the majority of patients with ASD developed mild-moderate COVID-19 disease, the long-term consequences of viral infection remain largely unpredictable.
- Direct and/or immune-mediated organ damages of COVID-19 infection represent a major challenge; both severe interstitial lung involvement that may evolve to fibrosis and diffuse microangiopathy seem to reproduce typical pathological features observable in the course of various ASD, particularly the systemic sclerosis. In-depth pathogenetic studies are required to better clarify the possible virus interaction with host immune system and the mechanism(s) involved in the tissue injuries.
- In the clinical practice, shared clinical guidelines are highly advisable in order to identify ASD patients' subgroups at high risk of infection, such as CTD/vasculitis patients, which may deserve differentiated therapeutic protocols, as well as predictive parameters of worse outcomes.

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Contributors All authors contributed to the conception and to the draft of the work, revised it critically for important intellectual content and gave the final approval of the version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Ferri C, Giuggioli D, Raimondo V, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-219113

Received 14 September 2020
Accepted 16 September 2020

Ann Rheum Dis 2020;**0**:1–2. doi:10.1136/annrheumdis-2020-219113

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